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| EXAMINER | |
|---|---|
| SGAGIAS, MAGDALENE K | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 12/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/803,550 | FOGARTY, PATRICK | |
| | Examiner | Art Unit | |
| | Magdalene K. Sgagias | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *10/11/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *11-18 and 27-34* is/are pending in the application.

4a) Of the above claim(s) *19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-18 and 27-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**DETAILED ACTION**

1. Claims 11-22 and 27-34 are pending.

Applicant's election with traverse of the invention of group II, claims 11-18 and 27-34, on October 11, 2005 is acknowledged. The traversal is on the grounds that as stated in the MPEP &803, if search and examination of an entire application can be made without serious burden, the examiner must examine the entire application on the merits, even though the entire application includes claims to independent or distinct inventions. It is the applicants' position that it would not be unduly burdensome to perform a each on all of the claims together in the present application. But examiner disagrees that group I and II are related because group is drawn to a kit comprising a P element vector that is distinct and different from the method of group II of inserting a DNA into the genome of a rodent or rodent cells. This is not found persuasive because restriction requirements are set forth for reasons of patentable distinction between each independent invention so as to warrant separate search and search and search burden. Accordingly, the applicants traverse the restriction requirement. The applicants expressly reserve the right under USC 35 &121 to file a divisional application during the pendency of this application. The requirement is still deemed proper and is therefore made FINAL. Thus, claims 19-22 are withdrawn from further consideration as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in the reply filed on October 11, 2005.

***Claim Rejections - 35 USC § 101***

2. Claims 11-12, 16-17, 27-29 and 31-33 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. These claims are directed to a transgenic animal, the scope of which encompasses creation of a transgenic human. Humans are considered non-statutory subject matter. As such the recitation of the limitation "non-human" would be remedial. See 1077 O.G April 24, 1987.

***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 11-18 and 27-34, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inserting an exogenous nucleic acid into the genome of a mouse, comprising co-introducing directly a first nucleic acid sequence encoding a gene of interest operably linked to a promoter, wherein said nucleic acid sequence further comprises a P element recognized insertion sequences and a second nucleic acid sequence encoding a transposase into the testis of said mouse wherein first nucleic acid is inserted into the germline of said mouse and wherein said nucleic acid is transmitted to the offspring, does not reasonably provide enablement for the claimed method with respect to all other non-Drosophilidae animals including humans and cells obtained from these animals and humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claimed invention encompasses a method of inserting an exogenous nucleic acid into the genome of a non-Drosophilidae animal including human, comprising introducing into said animal any transposase recognized insertion sequence vector and a second vector comprising a transposase under conditions sufficient for transposition to occur and exogenous nucleic acid vector is inserted into the genome of any type of cell in the animal including germline transmission (see claims 1-14). Dependent claim 15 limits vector size range in length from about 50 to 150,000 bp, and dependent claims 16-18 limit the non-Drosophilidae animal species including human into a vertebrate mammal or rodent. Claims 27-34 encompass obtaining cells from said animals which contain P element transposase recognized 31 bp insertion sequences integrated into their genome.

In determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether a skilled artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are; the breadth of the claims, the nature of the invention, the state of the art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore,

skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

These factors are analyzed, in turn, and demonstrate that one of ordinary skill in the art will need to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

In the instant application, the factors set forth are; (a) the breadth of the claims, the nature of the invention and the unpredictability for practicing said method of introducing any transposase recognized insertion sequence vector comprising any exogenous nucleic acid co-introduced with a second vector comprising a transposase into any non-Drosophilidae animal including humans under conditions for transposition to occur so that said exogenous nucleic acid is integrated into the genome of said animals, cells obtained from these animals containing P element transposase recognized insertion sequence vector or polypeptide synthesis or gene therapy applications of said vectors; (b) the amount of sufficient guidance provided for practicing claimed method; and (c) a working example for practicing claimed method.

Claimed invention encompasses a method of inserting an exogenous nucleic acid into the genome of a non-Drosophilidae animal including human, comprising introducing into said animal any transposase recognized insertion sequence vector and a second vector comprising a transposase under conditions sufficient for transposition to occur and exogenous nucleic acid vector is inserted into the genome of any type of cell in the animal including germline transmission (see claims 1-14). Dependent claim 15 limits vector size range in length from about 50 to 150,000 bp, and dependent claims 16-18 limit the non-Drosophilidae animal species including human into a vertebrate mammal or rodent. Claims 27-34 encompass obtaining cells from said animals which contain P element transposase recognized 31 bp insertion sequences integrated into their genome and cells obtained from said animals and humans. Because these

claims encompass a wide range of nucleic acid conditions sufficient for transposition to occur so that the exogenous nucleic acid is inserted into the genome of non-Drosophilidae animals including humans and phenotypes associated with it and cells obtained from said animals, the detail of the disclosure provided by the applicant, in view of the prior art, must encompass a wide knowledge, so that one of skill in the art, at the time of the invention, would be able to practice the invention as claimed by the applicant, without undue experimentation being imposed on the skilled artisan. Given the lack of guidance provided by the specification this burden has not been met because it would have require undue experimentation for one of skill in the art to produce the other species animal(s) embraced by the claims with a P element transposase recognized insertion sequences vector and a transposase vector integrated into their genome and cells obtained from said animals without reasonable expectation of success.

The claims are directed to a method of producing transgenic non-Drosophilidae animals expressing P element recognized insertion sequences encoding a gene of interest into any cell type of said animals including the germline and a method of producing the same transgenic non-human mammal.

The specification teaches the production of transgenic mice that express P element recognized insertion sequences encoding the beta galactosidase reporter gene into every tissue examined such as testis, liver, spleen, heart, lung, brain and intestine (specification p 18-18). Specification also teaches that mating of said mice integrated vectors are heritable (specification p 19, last paragraph). However, the specification does not provide any guidance how to practice claimed method in any other non-Drosophilidae animal species including humans other than mice. The art teaches that DNA transposons proved to be remarkably useful as transgenic vectors as well as insertional mutagens in certain invertebratae species, however, the art also teaches that a number of transposon systems require specific host

proteins for transposition, which limits their mobility outside their natural hosts as noted by Izsvak et al, (p 94, 1st column and 2nd column, 2nd paragraph) (J Mol Biol 302: 93-102, 2000). Izsvak et al, noted also that there is extensive variation in the extent to which transposase stimulates integration between different species and between different cell lines of the same species (p 100, 2nd column, 2nd paragraph). This is also supported by the art of Castro et al, where they note that the molecular mechanisms that control P element transposition and determine its tissue specificity remain incompletely understood, although much information has been compiled about this element in the last decade (Genetica, 1292): 107-18, 2004, abstract). Given the state of the art it would appear that the germline transmission of the P element transposase insertion sequences vectors into the genome of any cell type including the germline is unpredictable in other non-Drosophilidae animals including humans other than the mice as taught by the applicant. Thus a skilled artisan would have required undue experimentation to practice claimed method as claimed in the instant application because neither the art of record nor the applicant has provided sufficient guidance to practice claimed method without a reasonable expectation of success.

Claimed invention also encompass a method of obtaining cells from said animals which contain P element transposase recognized 31 bp insertion sequences integrated into their genome as recited in claims 27-34. However, the specification lacks to provide guidance for such claimed method in any non-Drosophilidae animal species including humans and mice. The specification also contemplates that the subject methods of stable integration of exogenous nucleic acid into the genome of a target animal find use include gene therapy (specification, p 15, lines 10-30, p 16, lines 1-2). The mere capability to perform gene therapy in any non-Drosophilidae animal species is not enabling because a desired phenotype can not be predictably achieved by simply introducing transgene P element vectors as disclosed in the

specification. The art of gene therapy is unpredictable. Numerous factors complicate the gene the gene delivery art which would not have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into tissues, etc), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRMA produced, the stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically on the vector being used and the protein being produced. While progress has been made in recent years for in vivo, gene transfer, vector targeting in vivo to desired organs continuous to be unpredictable and inefficient. This is supported by numerous teachings in the art. Romano et al, (Stem Cells, 18:19-20, 2000) reporting on the recent developments of gene therapy, noted, (However, the real effectiveness of gene therapy programs is still in question. After a decade of clinical trials, the therapeutic applications of gene transfer technology are still at a rather preliminary stage" (p 19, abstract). The specification discloses that an advantage of the subject vector over other known nucleic acid vectors is that the subject vectors provide random insertion of a foreign nucleic acid, which is desirable in many applications (specification, p 22, lines 5-15). However, the art also teaches that random integration also increases the possibility of gene disruption, including disruption of genes involved in cell cycle or tumor suppression (p 105, 2nd column, 2nd paragraph, Richardson et al, Stem Cells, 20: 105-118, 2002). Even a year post filling of the instant application, Richrdson et al, note delivery remains a significant hurdle irrespective of cell type and/or repair mechanisms (p 106, 2nd column, last paragraph). It is noted that these reviews by the leaders in the field of gene therapy are about those gene therapy are about those gene therapy applications where the mechanism of action and some efficacy has been

determined in animal models and there may be some extrapolatable correlations indicating the therapeutic effects of a particular gene's encoded protein. In the instant case, the specification does not teach as to how a P element vector as described which have the capability to mobilize up to 150 Kb of DNA carrying a DNA sequence or of similar length with therapeutic efficacy into any target cell or tissue of any claimed non-Drosophilidae animal species. Furthermore, the specification does not provide any guidance as to what doses of a nucleic acid of subject vectors will be administered to target desired tissues or organs in any of the claimed animal species. While applicants specification supports efficient transfer of for in vivo tail vein injection or intratesticular or intramammary injection of subject vector into mice and rats, the specification fails teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient transfer is achieved by any route of delivery in other non-Drosophilidae animal species as claimed in the instant application. The specification fails to teach any specific targeting techniques, fails to provide any working examples, which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art, which would allow one of skill in the art to practice the claimed invention without undue experimentation.

Therefore, limiting the scope of the claimed invention to a method of inserting an exogenous nucleic acid into the genome of a mouse comprising introducing into said mouse a P element transposase recognized insertion sequence vector and a second vector comprising a transposase and wherein said vectors are inserted into the genome of mouse and wherein integration occurs in every cell type, tissue type and organ examined and integrated vectors are heritable in mice.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 is indefinite as written. The claim depends from cancelled claim 1.

Claim 16 recites the limitation "target animal" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 17 recites the limitation "vertebrate animal" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 18 recites the limitation "mammalian animal" in line 1. There is insufficient antecedent basis for this limitation in the claim.

***Claim Rejections - 35 USC § 102***

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 11-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Dupuy et al, (Genesis, 30: 82-88, June 2001).

Dupuy et al, teaches the utilization of the pCAGGS-SB10 expression vector to create transgenic FVN/n strain mice that ubiquitously express the SB10 transposase (p 82, 2nd column, results). When doubly transgenic males expressing the Sleeping Beauty transposase gene (SB10) and harboring and harboring poly(A)-trap transposon vectors, were outcrossed to wild

type females, offspring were generated with new transposon insertions. These new insertions can be passed through the germline to the next generation and can insert into or near genes. Therefore, the claimed invention is aniticipated by Dupuy et al.

Claims 11-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Raz et al, (Current Biology, 8: 82-88, 1997).

Raz teaches a method of inserting the Tc3 transposon construct when supplied with the Tc3A transposase into the zebrafish genome (p 83 1st column and figure 1). Tc3 transposons carrying sequences encoding the green fluorescence protein (GFP) were able to integrate in the fish genome by transposition. Intergated transposons expressed the GFP marker after germline transmission, and were capable of being mobilized upon introduction of transposase protein in trans. Therefore, the claimed invention is anticipated by Raz et al.

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27-34, rejected under 35 U.S.C. 103(a) as being unpatentable over Clough et al, (Mol Cell Biol, 5(4): 898-901, 1985) in view of Rio et al, (J Mol Biol, 200:411-415, 1998 or Cell 44: 21-32, 1986 or Rio TIG 7: 282-287, 1991).

Clough et al, teaches a gene transfer vector containing the herpes simplex virus type 1 thymidine kinase (TK) gene flanked by Drosophila P element terminal repeats (p 899, figure 1).

This vector was introduced into mouse LTK-cells and enhanced the frequency of stable transformation to the TK+ phenotype by approximately 50-fold relative to a similar plasmid lacking the P element terminal repeats (p 899, Table1). At the time of the instant application an artisan of skill in the art would have been motivated to introduce this vector into mouse embryos because Clough et al, teaches this system provides means of enhancing the transfer of a variety of genes into mammalian cells of different types and into mammalian embryos (p 900, 2nd column, 1st paragraph).

The cited art does not teach that the vector further comprises sequences that encode transposase enzyme and that the transposase recognition sequences are 31 base pair long.

Both the Rio articles teach vectors that comprise P element recognition sequences flanking a sequence (J Mol Biol, p412, figure 1 and TIG, p 283). Additionally, Rio et al, teaches that P elements will be good genetic tools to use in other organisms where classical genetics is tedious. They further teach transposase activity in yeast and animal cells using an expression vector.

At the time of the invention it would have been obvious to include the transposase encoding sequences taught by Rio et al in the vector of Clough or to provide the transposase encoding sequences in a separate vector with a reasonable expectation of success. An artisan of skill would have been motivated to include transopsase coding sequences in the expression vector because this would eliminate the administration of the protein to a cell separately and introduce this vector into a mouse embryo because Clough teaches that this system provides a means of enhancing the transfer of genes into mammalian embryos.

***Conclusion***

8. **No claim is allowed**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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